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Does Aggressive Glycemic Control Benefit Macrovascular and Microvascular Disease in Type 2 Diabetes?: Insights from ACCORD, ADVANCE, and VADT

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Abstract Diabetes is increasing rapidly worldwide and frequently results in severe vascular complications. A target glycated hemoglobin of less than 7% has commonly been recommended in hopes of preventing both macrovascular and microvascular complications. Although results from trials of intensive glycemic control have generally supported the notion that lower glycated hemoglobin values reduce microvascular disease, the evidence for similar benefits for macrovascular disease has been less clear. As macrovascular disease is the major cause of morbidity and mortality in type 2 diabetes, this remains one of the more important unresolved clinical questions. Recent results from the ACCORD, ADVANCE, and VADT studies have challenged the conventional believe that lower glycated hemoglobin values should be pursued in all diabetic patients. Factors that may influence whether intensive glucose management is advisable include duration of diabetes, pre-existing macrovascular disease, hypoglycemic unawareness, and significant comorbidities. Glycated hemoglobin goals should account for these factors and be individualized for each patient.

Keywords Type 2 diabetes · Macrovascular disease · Microvascular disease · Intensive glycemic control · UGDP · UKPDS · ACCORD · ADVANCE · VADT · Coronary artery calcium · Atherosclerosis · Diabetes duration · Hypoglycemic unawareness · Glycated hemoglobin · Advanced glycation end products · Metabolic memory

Clinical Trial Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
DCCT	Diabetes Control and Complications Trial
UGDP	University Group Diabetes Program
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial

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Introduction

By the year 2030, it is estimated that 366 million people worldwide will have diabetes mellitus [1]. This predicted increase parallels the advancing age of the population, rising rates of obesity throughout the world, and sedentary lifestyles. Diabetes can result in significant macrovascular

and microvascular complications. Coronary artery disease, peripheral vascular disease, and stroke are well-recognized macrovascular complications, whereas retinopathy, nephropathy, and neuropathy are the more common microvascular disease manifestations.

The impact of hyperglycemia and its association with macrovascular disease has been examined in numerous studies. Several cohort studies, including the Diabetes Intervention Study [2], the San Antonio Heart Study [3], and the Framingham Study [4], have demonstrated a two- to fourfold increase in cardiovascular disease risk associated with either elevated glycated hemoglobin or fasting glucose. The consequences of cardiovascular disease are greater in patients with diabetes because death after acute myocardial infarction is 50% more common [5] and congestive heart failure is more common after acute myocardial infarction compared with nondiabetic patients [6]. Cardiovascular disease and stroke account for the highest percentage of deaths in people with diabetes even when other risk factors such as smoking, hyperlipidemia, and hypertension are considered.

Intensive glycemic control has been suggested as an effective treatment to reduce the burden of both macrovascular and microvascular disease. Until recently, guidelines by most health organizations have recommend a glycated hemoglobin goal of 7% or below without clear guidance as to whether other patient characteristics such as duration of diabetes, patient frailty, presence of pre-existing vascular disease, or concomitant illnesses should modify this goal. However, the optimal goal for glycemic control has been disputed since the publication of results from several recent studies including ACCORD, ADVANCE, and VADT.

This article reviews earlier studies as well as recent pivotal studies to help place these many diverse findings into a broader clinical context. An additional goal of this review is to help identify which subgroups may or may not benefit from more aggressive glycemic control.

Earlier Studies in Type 2 Diabetes: UGDP and UKPDS

UGDP

The UGDP completed in 1969 was one of the first randomized controlled trials conducted to assess the benefit of lowering blood glucose on the incidence of diabetes complications [7]. A total of 823 type 2 diabetic patients were randomly assigned to placebo, sulfonylurea (tolbutamide), or insulin to determine if use of a hypoglycemic agent could decrease vascular complications compared with placebo and insulin. The study failed to demonstrate a benefit for cardiovascular risk reduction. In fact, patients on tolbutamide had a higher rate of death from cardiovascular causes (12.7% vs 4.9%) than the placebo group. Even though there has been widespread criticism of UGDP, this study was one of the first to raise concern about glycemic management and its impact on cardiovascular mortality.

UKPDS

The UKPDS randomized 4209 patients with newly diagnosed type 2 diabetes in 23 centers within the United Kingdom between 1977 and 1991 [8]. Consistent with their recent diagnosis of diabetes, participants were younger than those in ACCORD, ADVANCE, and VADT with a mean age of 53.3 years (Table 1). Baseline mean glycated hemoglobin was similar to mean entry values in the ADVANCE study at 7.1% but lower than those found in ACCORD and VADT studies. Participants in the UKPDS were assigned to receive conventional therapy with dietary restriction or intensive therapy (either sulfonylurea or insulin, or, in overweight patients, metformin). The UKPDS was designed to establish whether intensive blood glucose control reduced the risk of macrovascular or microvascular complications in type 2 diabetes. Although glucose levels fluctuated over the 10-year study duration, the median glycated hemoglobin in the intensive group was 7.0% compared with 7.9% in the conventional group. Intensive glycemic therapy was associated with a 25% reduction in microvascular disease; however, most of this reduction was attributed to fewer patients requiring photocoagulation. There was a nonsignificant reduction in relative risk of myocardial infarction (16% risk reduction; $P=0.052$), but no overall decrease in macrovascular disease. In subgroup analyses of intensive therapy patients allocated to metformin there was a risk reduction of 32% ($P=0.0023$) for any diabetes-related end point including macrovascular and microvascular complications, a 42% risk reduction ($P=0.017$) for diabetes-related death, and a 36% risk reduction for all-cause mortality ($P=0.011$) compared with the conventional group. This data suggests that intensive glucose control with metformin appears to decrease the risk of diabetes-related end points in overweight diabetic patients [9].

UKPDS Follow-Up

After completion of the active intervention study, differences in glycated hemoglobin levels between the standard and intensive glycemic groups disappeared after the first year. Participants were followed for an additional 10 years, either at annual clinic visits for the first 5 years, or with follow-up questionnaires subsequently. In the combined group assigned to treatment with either sulfonylurea or insulin, persistent and now significant relative risk reduc-

Table 1 Baseline and on-study characteristics of subjects in the UKPDS, ACCORD, ADVANCE, and VADT studies

	UKPDS		ACCORD		ADVANCE		VADT	
Baseline characteristics								
N	3867		10,251		11,140		1791	
Gender male/female (%)	61/39		61/39		57/43		97/3	
Mean age (y)	53.3		62.2		65.8		60.4	
Duration of diabetes (y)	Newly diagnosed		10		8		11.5	
History of macrovascular disease (%)	6		35		32		40	
Mean HbA_{1c} (%)	7.1		8.3		7.5		9.4	
On insulin (%)	0		35		1.5		52	
Study protocol	Intensive	Standard	Intensive	Standard	Intensive	Standard	Intensive	Standard
HbA_{1c} goal (%)	FPG <108 mg/dL	Best achievable with diet	<6	7.0–7.9	≤ 6.5	Goal based on local guidelines	<6 (action if > 6.5)	Planned separation of 1.5
Treatment strategy	Sulfonylurea, insulin, metformin	Diet, if FPG > 270 mg/dL then addition of drugs	Different glucose-lowering agent and/or insulin at the discretion of physician		Gliclazide + other treatment at the discretion of physician	No gliclazide, other treatment at discretion of physician	BMI > 27 kg/m^2: max dose of metformin + rosiglitazone. BMI <27 kg/m^2: glimepiride + rosiglitazone. Insulin if HbA_{1c} of ≥ 6%	Half doses of intensive treatment. Insulin if HbA_{1c} ≥ 9%
On-study characteristics								
Median follow-up (y)	10	10	3.4	3.4	5.0	5.0	5.6	5.6
Median HbA_{1c} achieved	7.0[a]	7.9[a]	6.4	7.5	6.5	7.3	6.9	8.4
On insulin at study end (%)	55	23	77	55	41	24	NS	
On TZD at study end (%)	NS	NS	91	58	17	11	53	42
On statin at study end (%)	NS	NS	88	88	46	48	85	83
On aspirin at study end (%)	NS	NS	76	76	57	55	88	86
Mean blood pressure at study end (mm Hg)	NS	NS	126/67	127/68	136/74	138/74	127/69	125/69
Weight changes (kg)	NS	NS	+3.5	+0.4	−0.1	−1.0	+7.8	+3.4

[a] Median achieved HbA1c over 10 years

ACCORD Action to Control Cardiovascular Risk in Diabetes; *ADVANCE* Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; *BMI* body mass index; *FPG* fasting plasma glucose; *HbA1c* hemoglobin A1c; *NS* not stated; *TZD* thiazolidinedione; *UKPDS* United Kingdom Prospective Diabetes Study; *VADT* Veterans Affairs Diabetes Trial

tions of 15% for myocardial infarction and 13% for death of any cause were seen as more events occurred over time [10••]. Furthermore, the significant reduction of 25% in the risk of microvascular disease observed during the interventional trial in the intensive therapy group persisted throughout the post-trial period (Table 2).

Thus, the UKPDS showed a benefit of improved glycemic control in reducing the risk of microvascular disease during the interventional trial, but the risk reduction for myocardial infarction and death from any cause were observed only with extended post-trial follow-up. Persistent and long-term benefits for microvascular disease reduction noted in the post-trial UKPDS follow-up, despite the early loss of within-trial differences in glycated hemoglobin between the intensive therapy group and the conventional therapy group in the first year after trial completion, have been termed a "legacy effect." One of the proposed concepts to explain this purported extended legacy effect is metabolic memory. This is the concept whereby the early glycemic environment is remembered by target organs and affects future vascular changes [11–13]. The legacy effect is also supported by long-term monitoring data after completion of the DCCT. Results from this epidemiologic follow-up demonstrated that prior intensive diabetes therapy in type 1 diabetes reduced the risk of any cardiovascular disease event by 42% (P=0.02) and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57% (P=0.02) [14].

ACCORD

The ACCORD trial was specifically designed to determine whether targeting normal glycated hemoglobin levels (<6.0%) would reduce the rate of cardiovascular events compared with targeting levels from 7.0% to 7.9% in type 2 diabetic patients with established cardiovascular disease or additional risk factors [15••]. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After recruitment, 10,251 participants were randomized to receive intensive glucose-lowering therapy with oral agents, insulin, or both to achieve specified glycated hemoglobin values. Participants had long-standing diabetes (~10 years), a mean age of 62.2 years, and a mean glycated hemoglobin level of 8.3% (Table 1). Previous cardiovascular events were reported in 35% of the study participants. Intensive and standard therapeutic strategies rapidly achieved differ-

Table 2 Outcomes for subjects in the UKPDS, ACCORD, ADVANCE, and VADT studies

Outcomes				
	UKPDS	ACCORD	ADVANCE	VADT
Primary outcome	Aggregate of any diabetes-related end point, diabetes-related death, all-cause mortality	Composite of nonfatal MI, nonfatal stroke, and CV death	Composite of major macrovascular and microvascular events	Composite of major CV events
Risk for primary outcome (95% CI)	RR any diabetes-related end point 0.88 (0.79–0.99) RR diabetes-related death 0.90 (0.73–1.11)	HR 0.90 (0.78–1.04)	HR 0.90 (0.82–0.98)	HR 0.88 (0.74–1.05)
Risk for total mortality (95% CI)	RR 0.94 (0.8–1.1)	HR 1.22 (1.01–1.46)	HR 0.93 (0.83–1.06)	HR 1.07 (0.81–1.42)
Risk for CV mortality (95% CI)	NS as combined end point RR fatal MI 0.94 (0.68–1.30) RR fatal stroke 1.17 (0.54–2.54)	HR 1.35 (1.04–1.76)	HR 0.88 (0.74–1.04)	HR 1.32 (0.81–2.14)
Risk for nonfatal MI (95% CI)	RR 0.79 (0.58–1.09)	HR 0.76 (0.62–0.92)	HR 0.98 (0.78–1.23)	NS
Risk for nonfatal stroke (95% CI)	RR 1.07 (0.68–1.69)	HR 1.06 (0.75–1.50)	HR 1.02 (0.85–1.24)	NS
Risk for microvascular disease (95% CI)	RR 0.75 (0.6–0.93)	NS	HR 0.86 (0.77–0.97)	NS
Follow-up studies				
	Microvascular intensive	Microvascular intensive	Macrovascular intensive	Macrovascular intensive
UKPDS	Sulfonylurea-insulin	Metformin	Sulfonylurea-insulin	Metformin
	After 16.8 y, 25% relative reduction in risk of microvascular complication	No significant risk reductions during or after the trial in microvascular disease	After 16.8 y, 15% risk reduction for MI 13% risk reduction from death of any cause	After 17.7 y, 33% risk reduction in MI, 27% reduction from death of any cause
ACCORD			After 5 y, reduced nonfatal MIs but increased 5-y mortality	

ACCORD Action to Control Cardiovascular Risk in Diabetes; *ADVANCE* Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; *CV* cardiovascular; *HR* hazard ratio; *MI* myocardial infarction; *NS* not stated; *RR* relative risk; *UKPDS* United Kingdom Prospective Diabetes Study; *VADT* Veterans Affairs Diabetes Trial

ent glycated hemoglobin levels, and within 4 months of randomization the level had fallen from 8.1% at baseline to 6.7% in the intensive therapy group and to 7.5% in the standard therapy group. At 1 year, stable median levels of 6.4% in the intensive group and 7.5% in the standard group had been achieved and were maintained until increased mortality was observed in the intensive therapy group. Differences in mortality emerged 1–2 years after randomization. Compared with the standard therapy group, the intensive therapy group had a relative increase in mortality of 22%. The finding of higher mortality in the intensive therapy group led to discontinuation of intensive therapy after a mean of 3.5 years of follow-up. The increase in mortality was equivalent to approximately one extra death (primarily from cardiovascular causes) for every 95 patients treated for 3.5 years. As a result of these findings, intensive therapy group subjects were subsequently transitioned to standard therapy and followed until study completion (median of 5 years). After this transition, the median glycated hemoglobin level in the intensive group rose from 6.4% to 7.2%.

The lower glycated hemoglobin levels in the intensive therapy group were associated with a greater exposure to diabetes medications and participants within this group had more frequent changes in the dose or the number of study drugs used. In contrast to the standard therapy group, the intensive therapy group had significantly higher rates of hypoglycemia, weight gain, and fluid retention. Although many explanations for the increased mortality in ACCORD have been proposed, including rapid reduction of high glycated hemoglobin values or maintenance of glycated hemoglobin at near-normal levels, hypoglycemia, effects of drugs or drug combinations, and weight gain [16], none have been definitively supported in post hoc analyses. Of note, analyses by Riddle et al. [17] have implicated factors associated with persistent higher glycated hemoglobin levels rather than low glycated hemoglobin levels as likely contributors to the increased mortality associated with intensive glycemic control. Specifically, the risk of death appeared to be greater with intensive glycemic control compared with the standard therapy group only when the average glycated hemoglobin was greater than 7%.

ACCORD Macrovascular Results

At 3.5 years of follow-up, the primary outcome occurred in 352 participants in the intensive therapy group compared with 371 participants in the standard therapy group (Table 2; hazard ratio, 0.90; P=0.16). Thus, the use of intensive therapy to target normal glycated hemoglobin levels resulted in increased mortality and did not significantly reduce major cardiovascular events. As previously mentioned, participants in the intensive therapy group were transitioned to the standard therapy regimen and followed for the remaining 17 months to complete the planned 5-year trial. At the end of the 5-year trial, the median glycated hemoglobin levels were 7.2% in the intensive therapy group and 7.6% in the standard therapy group. The overall rate of nonfatal myocardial infarction in the intensive therapy group was lower than in the standard therapy group (1.18% vs 1.42%; hazard ratio, 0.82; 95% CI, 0.70–0.96; P=0.01) [18••]. However, analysis at the end of 5 years showed a 19% higher rate of death from any cause in the intensive therapy group compared with the standard therapy group (1.53% vs 1.27%; 95% CI, 1.03–1.38; P=0.02). There were no clear differences in any of the other predefined cardiovascular outcomes. Thus, the use of intensive therapy for 3.5 years to target a glycated hemoglobin level below 6% reduced 5-year nonfatal myocardial infarctions but increased 5-year mortality. Based on results from ACCORD, a similar strategy of intensive glycemic control aiming toward a glycated hemoglobin of less than 6% cannot be recommended in patients with advanced type 2 diabetes and a high risk of cardiovascular disease.

Although there was no overall benefit for the whole group, prespecified subgroup analyses indicated there were fewer cardiovascular events in patients without a previous history of cardiovascular disease events (~5% vs 11%) or with a baseline glycated hemoglobin of 8.0% or less (~6% vs 8%). This indicates that participants with less “advanced” diabetes may in fact benefit from intensive glycemic control. In contrast, those with pre-existing cardiovascular disease or higher baseline glycated hemoglobin levels may be at greater risk of cardiovascular events if aggressive glycemic control is rapidly achieved following the ACCORD approach.

ACCORD Microvascular Results

ACCORD also had predefined secondary end points to assess the effect of intensive therapy on the incidence and progression of retinopathy, nephropathy, and neuropathy. Composite outcomes of advanced nephropathy, diabetic eye complications, and neuropathy did not differ between groups at the point of transition or at the official study end. However, intensive therapy was associated with a 21% reduction in the development of microalbuminuria at the point of transition and a 15% reduction at the end of the 5-year study. Furthermore, the risk of development of macroalbuminuria was 31% lower with intensive therapy at transition and 28% lower at study end. Macroalbuminuria is a known risk factor for renal insufficiency [19] and cardiovascular disease [20]. These findings support the

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